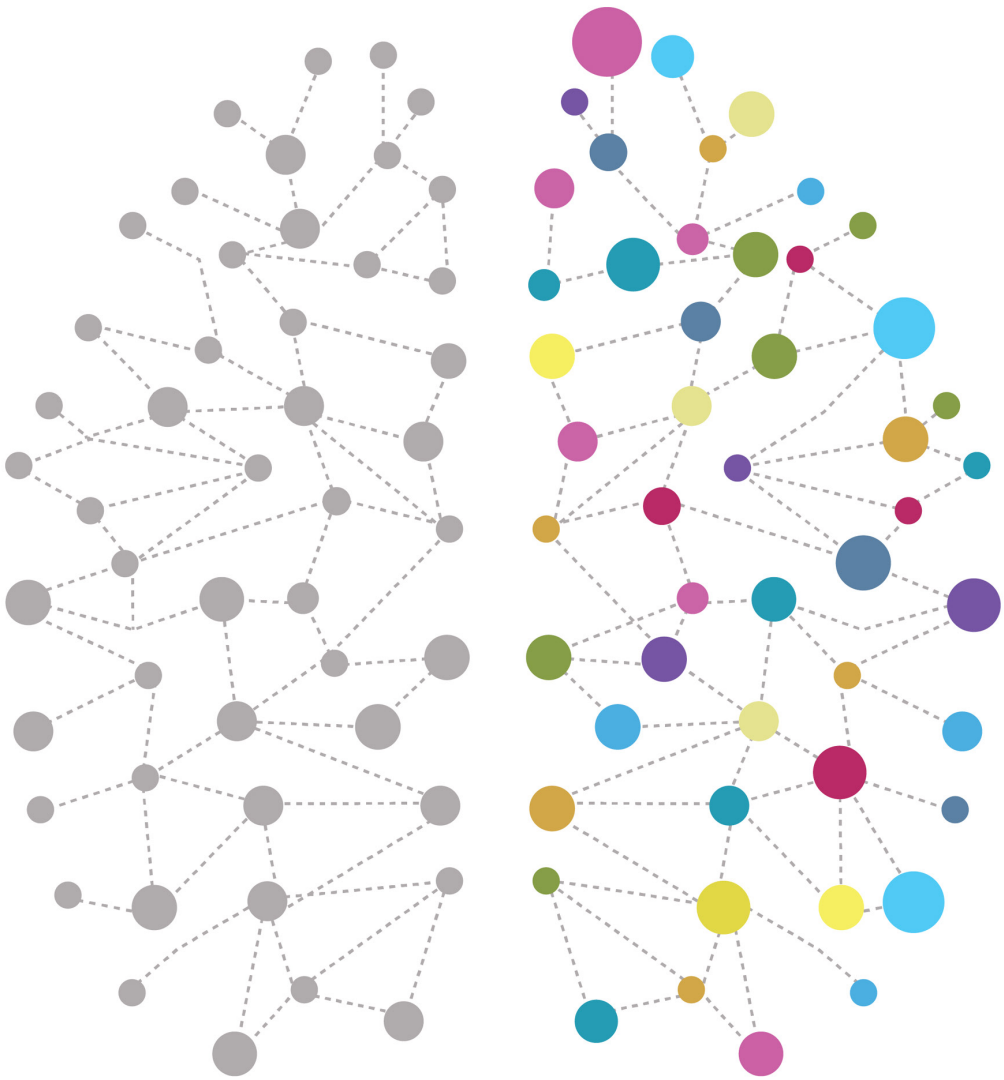
WHITE PAPER

eleusis

Lysergic Acid Diethylamide as a Multi-Target Therapeutic for Alzheimer's Disease



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INTRODUCTION

Alzheimer's Disease (AD) is a heterogenous neurodegenerative disease expected to afflict nearly 15 million people over 65 in the US by 2050 (Alzheimer's Association, 2020). Mild cognitive impairment (MCI) is a prodromal state of AD, associated with amnesic cognitive dysfunction distinct from normal aging. The progression of MCI to AD features multiple dysregulated physiological cascades that characteristically feature the accumulation of abnormally folded amyloid-β (Aβ) and tau proteins in amyloid plaques and neurofibrillary tangle deposits[1]. The multifactorial nature of early-stage AD suggests multiple pathophysiological processes, including neuroinfammmation[2], synaptic degeneration[3], neuropsychiatric/neurendocrine dysfunction[4,5] and brain insulin resistance[6], all of which are potential targets for therapeutic intervention.

Targeted immunotherapies capable of disease modification by reducing Aβ and tau burden have failed to influence AD progression in late-stage clinical trials, and the only FDA-approved drug therapies are symptomatic in nature with marginal and transient clinical efficacy, highlighting the urgent need for new approaches to disease modification[7,8]. Multi-targeted drugs (MTDs) with established safety profiles could empirically engage identified therapeutic targets[9].

We propose the hypothesis that low-dose lysergic acid diethylamide (LSD) represents a promising disease modifying therapeutic for AD. LSD is a classic psychedelic drug and is one of the most well-studied psychoactive drugs in the history of modern pharmacology[10,11] and shares structural similarity to 5-HT (**FIGURE 1**).

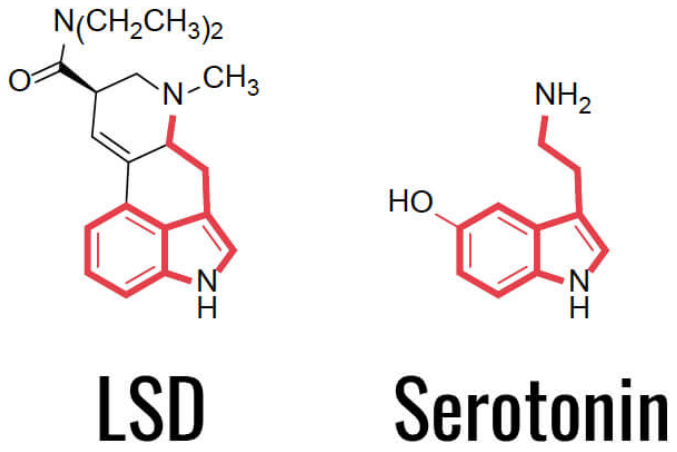

FIGURE 1. illustrations of 5-HT and LSD, highlighting their similarities in structure in color (Adapted from Nichols DE. Serotonin, and the Past and Future of LSD. *MAPS Bulletin* Spring 2013).

This article sets out the evidence and arguments for why the pharmacology of LSD, when administered at sub-psychoactive doses, makes it an appealing disease-modifying therapeutic candidate for AD, and provides background for the design and conduct of further studies to evaluate its efficacy.

SEROTONINERGIC SYSTEM IN AGEING AND AD

5-HT is a monoamine neurotransmitter and hormone that exerts a direct modulatory influence on nearly all the pathological, physiological and behavioral changes observed in AD[12,13]. Preclinical and clinical data suggest that modulating 5-HT receptors may be a useful therapeutic strategy for AD, eg. Selective serotonin reuptake inhibitors (SSRIs) preserve cognition, suppress microglial activation, and lower brain Aβ levels in AD animal models[14-17], while long-term SSRI use (> 4 years) delays the conversion of MCI to AD in MCI patients[18]. Because SSRIs do not demonstrate a robust disease modifying effect in depressed MCI patients, it is possible that the indiscriminate activation of all 5-HT receptors in the CNS by 5-HT could result in opposing effects. Instead, selective activation of only relevant 5-HT receptors may maximize therapeutic value of 5-HT receptor targeted therapeutics.

LSD binds to a subset of serotonin (5-HT), dopamine and other biogenic amine receptors with different affinities. The biological effect of LSD is related to its receptor binding and occupancy, which in turn is governed by the concentration of LSD to which the receptor is exposed. At low, sub-psychoactive doses, LSD selectively occupies several of the 5-HT receptor subtypes (see heatmap in **TABLE 1**).

SEROTONINERGIC SYSTEM IN AGEING AND AD (CONT'D)

Receptor Target	NE B1	NE B2	DA 2	DA 3	DA 4	DA 5	Hist 1	5-HT 1A	5-HT 1D	5-HT 1E	5-HT 2A	5-HT 2B	5-HT 2C	5-HT 5A	5-HT 6	5-HT 7
Apparent affinity (-pKi)	6.9	6.1	6.9	7.6	7.3	6.5	5.8	8.9	8.4	7.0	8.4	7.5	7.8	8.1	8.2	8.2
LSD concentration	**Poly-pharmacological Profile (receptor sites occupancy in %)**															
10 nM	7	1	8	27	15	3	1	90	72	10	69	25	38	53	60	61
1 nM	1	0	1	4	2	0	0	47	20	1	18	3	6	10	13	13
0.1 nM	0	0	0	0	0	0	0	8	3	0	2	0	1	1	1	2

TABLE 1. Estimated polypharmacological profile of LSD shows the fraction of each receptor type that is saturated or bound by LSD
Occupancy at different theoretical concentrations of LSD was estimated by the Hill-Langmuir equation assuming a Hill coefficient of 1 and using the average experimental Ki values for apparent affinity at human receptors in cellular models. Source of Ki information: CHEMBL (accessed April 2020)
NE, norepinephrine; DA, dopamine; Hist, histamine, 5-HT, serotonin

LSD is qualitatively distinct from 5-HT in that it differentially modulates 5-HT receptors, possessing partial agonist, agonist and antagonist properties at the various 5-HT receptor subtypes with the exception of the 5-HT_3 and 5-HT_4 receptors, and is quantitatively different in its activation profile, depending on dose[11]. We have recently demonstrated the safety and tolerability of chronic low dose LSD (i.e. doses up to 20 µg) in healthy elderly volunteers[19]. In this study, no physiological or behavioral effects significantly differed from placebo and pharmacokinetic evaluation suggest that plasma levels are in a nanomolar concentration range consistent with moderate occupancy and a more subtle engagement profile at 5-HT receptors in the brain, devoid of excessive pharmacology hallmarks (**FIGURE 2**, **Table 1** see 1 nM row of polypharmacological profile). We propose that the functional selectivity and potency of LSD at 5-HT_{2A} receptors, which underlies its neuropsychological psychedelic properties at higher doses[20], together with its selective modulation of certain other 5-HT and dopamine receptors, represents a novel polypharmacological-based strategy for the disease modification of AD.

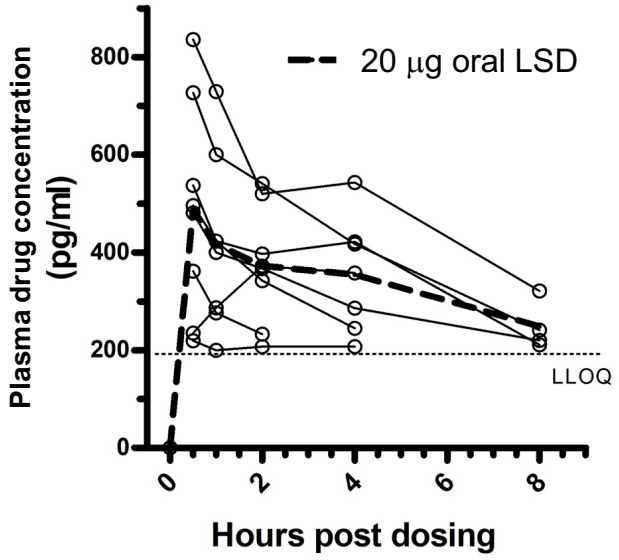

FIGURE 2. Plasma drug levels of LSD in humans after administration of a non-psychedelic "microdose" of LSD.
The average C_{Max} in plasma was 0.44 ng/ml, which is equivalent to 1.5 nanomolar (nM) concentrations. The dotted line represents the mean per dosing group from baseline to 8 h post-dose (adapted from: Family et al., *Psychopharmacology (Berl)*. 2020 Mar;237(3):841-853)
LLOQ, lower limit of quantification

PRIMARY TARGET: THE 5-HT_{2A} RECEPTOR

5-HT_{2A} receptors exhibit the highest expression in cortical and subcortical areas of the human brain relevant to AD pathobiology[18,21-25]. Polymorphisms in the 5-HT_{2A} receptor gene (*HTR2A*) are associated with vulnerability to AD[26] and differences in memory function[27-33], and cognitive impairment correlates with reductions in 5-HT_{2A} receptor expression[34]. In this section, we discuss roles of the 5-HT_{2A} receptor signaling relevant to AD pathobiology.

PRIMARY TARGET: THE 5-HT$_{2A}$ RECEPTOR (CONT'D)

5-HT$_{2A}$ and Amyloid Precursor Protein (APP) Metabolism

MCI patients have alterations in APP processing which lead to accumulation of Aβ and plaques that correlate with reduced cortical 5-HT receptors[35]. Conversely, in an animal model of streptozotocin-induced memory deficits, the potent 5-HT$_{2A}$ agonist, TCB-2, reduced Aβ burden[36], while in another model (McGill-R-Thy1-APP model of APP overexpression[37]) reductions in soluble Aβ40 and Aβ42 have been recorded following chronic administration of LSD at 0.1 mg/Kg (Eleusis unpublished data). These observations are consistent with the premise that 5-HT$_{2a}$R activation exerts a therapeutic influence on Aβ accumulation.

5-HT$_{2A}$ Receptors and Neuroplasticity

Aging is associated with decreases in neuroplasticity[38,39], and age is a primary risk factor for dementia[40]. Age-related decline in neuroplasticity may significantly contribute to synaptic and neuronal loss in AD[41,42]. One of the key molecules underlying synaptic plasticity and for which expression is associated with slower cognitive decline in aging is Brain Derived Neurotrophic Factor (BDNF)[43]. Decreased BDNF receptor (TrkA and TrkB) expression has been associated with cognitive impairment, neurodegeneration, and increased Aβ plaque and neurofibrillary tangle burden in patients with AD[44,45]. Individuals with the ε4 ApoE allele variant, who have more susceptibility to MCI and conversion to AD[46,47], exhibit disproportionate and progressive hippocampal atrophy[48]. The neurodegeneration associated with ε4 ApoE is accompanied by reduced levels of both BDNF and 5-HT$_{2A}$ receptors[49]. Conversely, increased TrkB expression is associated with cognitive resilience despite detectable hippocampal AD-related pathology[50], and its protective properties on brain function may be associated with its role in increasing synaptic density and complexity[51].

Animal studies have demonstrated a complex relationship between 5-HT$_{2A}$ receptors, stress and BDNF that may impact neuroplasticity (**FIGURE 3**)[52]. Potent 5-HT$_{2A}$ receptor agonists upregulate mRNA expression of genes related to synaptic plasticity *in vivo*[53-55], as well as increase BDNF levels and attenuate hippocampal neurodegeneration and memory impairment in animal models of neurodegeneration[36]. 5-HT$_{2A}$ receptor agonists can also increase BDNF receptor expression in neuronal cells *in vitro*[56]. Collectively, these findings suggest that potent 5-HT$_{2A}$R activation by low dose LSD could at least slow the progressive neurodegeneration and memory impairment in MCI and early AD patients.

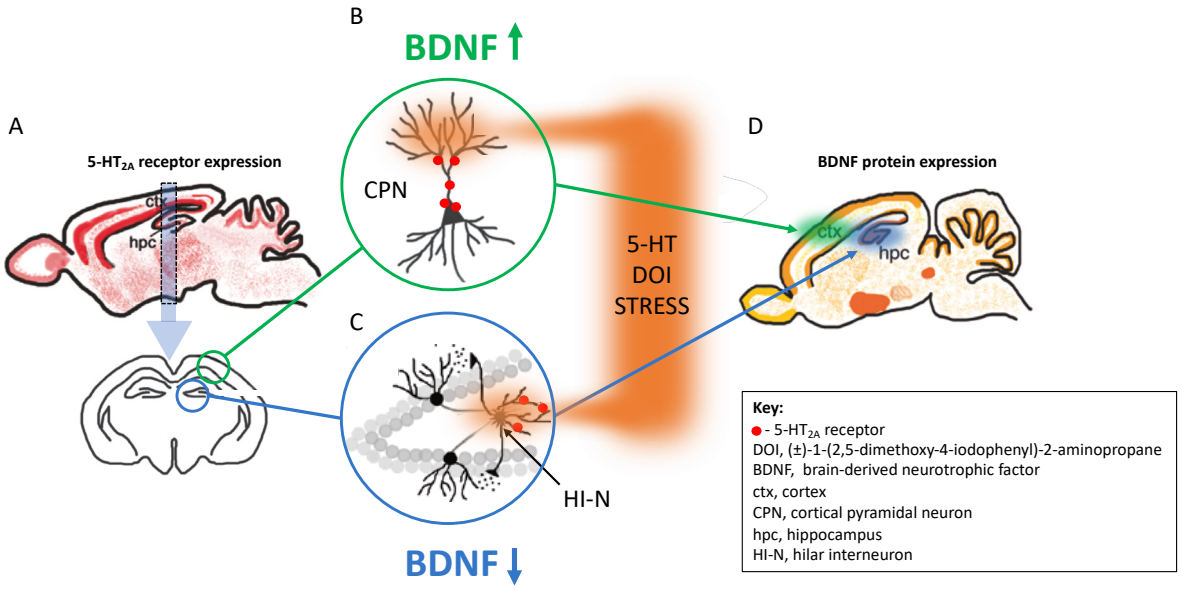

FIGURE 3. Model for 5-HT$_{2A}$-dependent modulation of BDNF in the CNS, illustrating how 5-HT could influence BDNF levels in either direction in the cortex or hippocampus. (A) Sagittal (top) and coronal (bottom) sections of the rodent brain: saggital section shows the expression pattern of 5-HT$_{2A}$ receptors; coronal section of the rodent brain highlights the neocortex (green circle) and hippocampus (blue circle). (B) Neocortical pyramidal neuron, expressing 5-HT$_{2A}$ receptors which can be activated by DOI, 5-HT and stress to enhance BDNF expression. (C) Hilar inhibitory interneuron in the hippocampus expressing 5-HT$_{2A}$ receptors, which can be activated by DOI, 5-HT and stress to evoke a decline in BDNF expression. (D) Saggital section of the rodent brain showing pattern of regional BDNF expression; the green and blue areas illustrate elevation and depression of BDNF in the neocortex and hippocampus, respectively, by DOI, 5-HT and stress. (Adapted from: Jaggar and Minal, 2018 5-HT$_{2A}$ Receptors and BDNF Regulation: Implications for Psychopathology. In: Guiard B., Di Giovanni G. (eds) 5-HT$_{2A}$ Receptors in the Central Nervous System. *The Receptors, vol 32*. Humana Press, Cham)

PRIMARY TARGET: THE 5-HT$_{2A}$ RECEPTOR (CONT'D)

5-HT$_{2A}$ Receptors and Insulin Resistance

Insulin resistance (IR) is an established risk factor for MCI and AD is also a core feature of Type 2 diabetes (T2D), and a disease that doubles the risk of AD[6,57,58]. Further, metabolic syndrome is associated with hypometabolism in key brain regions implicated in early AD progression[59], cognitive impairment, neuritic plaque burden, inflammation, oxidative stress, and hippocampal atrophy[60-62]. Impaired insulin receptor signaling in metabolic disease often involves dysfunction in insulin receptor substrate adaptor proteins responsible for glucose uptake and their effectors like AKT and has been associated with progression from MCI to AD, Aβ plaque burden, and cognitive decline[63-65].

In animal models, IR signaling and central 5-HT$_{2A}$ receptors appear to have a bi-directional relationship, whereby IR in the periphery results in increased cortical 5-HT$_{2A}$ receptor expression as well as 5-HT$_{2A}$ receptor-mediated behavior, and 5-HT$_{2A}$ receptor activity can also modulate insulin-related processes[66,67].

Together these observations suggest that further study of the role of 5-HT$_{2A}$ receptors and IR is merited to clarify if 5-HT$_{2A}$ agonists could have therapeutic efficacy relevant to brain IR and its associated pathobiological role in MCI and AD.

5-HT$_{2A}$ Receptors and Neuroinflammation

Neuroinflammation is primarily mediated by microglia in the brain, and has been strongly implicated in the pathobiology of AD[68]. Normally, adaptive beneficial microglial responses to AD pathobiology include Aβ phagocytosis and clearance, and the release of trophic and anti-inflammatory factors capable of supporting neuroplasticity and the resolution of acute inflammation[68]. However, microglia can switch and assume a pro-inflammatory, neurotoxic phenotype during the course of AD[68-70]. Animal studies have provided key insights into the deleterious effect of inappropriate microglial activation and shown that intracerebroventricular (ICV) injection of Aβ oligomers induces depressive-like behavior, reduces 5-HT and increases Tumor Necrotic Factor alpha (TNF-α) levels in the brain, which can be prevented by ICV 5-HT injection[71,72]. Microglia express 5-HT$_{1A}$, 5-HT$_{2A/B}$ and 5-HT$_{7}$ receptors[23,73] and a link between 5-HT$_{2A}$ receptor expression and neuroinflammation comes from animal data showing early life infection can result in persistent upregulation of 5-HT$_{2A}$ receptors in the brain into adulthood[74]. This is associated with increased depressive-like behaviors and hypersensitivity to the inflammatory effects of TNF-α and lipopolysaccharide[75]. LSD may attenuate neuroinflammation through direct modulation of receptors expressed on microglia themselves. Another pathway of anti-inflammatory effect could be mediated indirectly via modulation of the glucocorticoid system.

Astrocytes are the most abundant glial cell and play a diverse range of roles in the CNS, including support of neuroplasticity, neuronal metabolic support, and innate immunity, and may also be relevant to neuroinflammatory processes associated with AD[76]. Similar to microglia, reactive astrocytes in AD adopt a neurotoxic status and lose their neurotrophic abilities[76]. Astrocyte activation is a hallmark of late stage AD pathology, but MCI patients are also observed to present with elevated reactive astrocyte phenotype[77]. Reactive astrocytes in particular may be more susceptible to modulation by 5-HT$_{2A}$ receptor agonists, as increased astrocytic 5-HT$_{2A}$ receptor expression has been measured in post mortem AD brain tissue[78]. Excessive glucocorticoid receptor (GR) activation, as is seen with hypercortisolemia, reduces the neuronal support properties of astrocytes, especially in hippocampus[79], potentially compromising its function in cognition[80]. LSD and other 5-HT$_{2A}$ receptor agonists appear to attenuate hypercortisolemia through normalization of GR function[81] and thereby may protect astrocyte function.

Oxidative stress is believed to drive neuroinflammation and neurodegeneration in several diseases including AD. Mitochondrial dysfunction resulting in accumulation of reactive oxygen species can reduce trophic factors, including those necessary for glia to support neurons, and drive Aβ-associated pathobiology in AD[82]. 5-HT$_{2A}$ receptor agonists have been found to possess potent neuroprotective effects against oxidative stress in neuronal and non-neuronal cell lines as well as enhance mitochondrial function[83,84].

Collectively, these results indicate that LSD and other 5-HT$_{2A}$ receptor agonists may have broad-based neuroprotective potential as therapies in age-related neurodegenerative diseases like AD, in which life stress, inflammation, oxidative stress and mitochondrial dysfunction may all play a role.

5-HT$_{2A}$ Receptors and Epigenetic Regulation

Cognitive impairment has been associated with increased expression in the hippocampus in both aged and stressed animal models of histone deacetylase 2 (HDAC2)[85-91], an enzyme that regulates gene transcription by increasing the packing of chromatin, leading to transcriptional

silencing. HDAC2 overexpression can also lead to impaired memory function and neuroplasticity[92]. In contrast, suppression of HDAC2 activity can have beneficial effects that include enhancement of associative learning and fear extinction[93] and is neuroprotective[94]. In animal models, AD-related neurotoxicity increases the HDAC2 blockade of neuroplasticity gene transcription, and in AD patients[86]. HDAC2 expression is found to be increased in early stage AD post mortem brain, with progressive elevation of expression in the hippocampal CA1 and entorhinal cortex regions[86,95]. Increased HDAC2 levels are also associated with increased tau and reduced neuroplasticity in AD animal models[96].

Evidence that 5-HT$_{2A}$ receptor signaling in the brain is influenced by epigenetic processes relevant to AD is complex, but atypical antipsychotics and other 5-HT$_{2A}$ receptor antagonists can increase HDAC2 expression and activity, producing reductions in synaptic spine density and impaired cognitive function[97,98]. A mechanism by which they do this involves downregulating an HDAC2 gene repressor, IκBα, which results in augmentation of HDAC2 levels[97]. Conversely, LSD and other 5-HT$_{2A}$ receptor agonists can significantly increase brain expression of IκBα[54,55,97,99], thereby repressing HDAC2 expression and activity with the potential for enhancement of cognitive and neuroprotective processes.

Sirtuin-1 (SIRT1), another histone deacetylase protein encoded by the *SIRT1* gene, also plays a significant role in AD pathology[100]. Reduced SIRT1 expression is observed in post-mortem AD patient brains in association with tau burden and cognitive impairment[101] and progressive decline in SIRT1 serum concentrations have been observed in MCI and AD patients[102]. Consistent with these observations, elevated SIRT1 expression is associated with preserved cognitive function in AD[103]. In animals, 5-HT$_{2A}$ receptor activation is associated with neuroprotection in a SIRT1 dependent manner, likely contributing to the neuroprotective properties of 5-HT[104] (**FIGURE 4**).

Together, these findings suggest that LSD and other 5-HT$_{2A}$ receptor agonists could ameliorate neuronal mitochondrial dysfunction in MCI and/or AD through epigenetic pathways associated with HDAC2 and SIRT1.

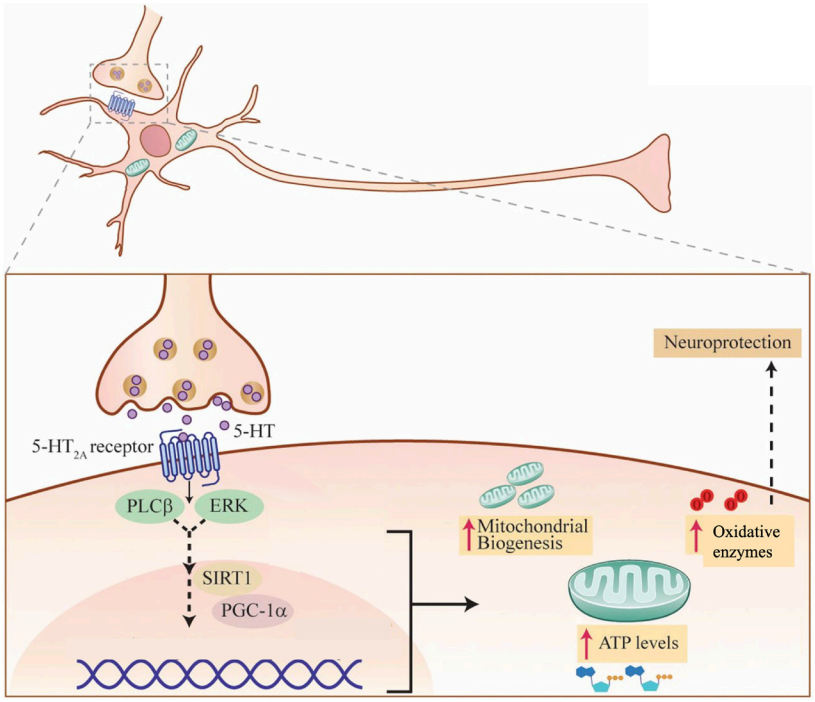

FIGURE 4. Model of possible mechanism for 5-HT influence of neuroprotection. 5-HT or 5-HT$_{2A}$ agonists bind to the 5-HT$_{2A}$ receptor expressed on cortical neurons, recruits SIRT1 via PLC and MAPK signaling pathways. SIRT1 in turn interacts with the key regulator of mitochondrial biogenesis, PGC-1α. 5-HT and 5-HT$_{2A}$ receptor agonists also enhance ATP production, respiratory capacity and antioxidant enzymes. levels and enhances expression of antioxidant enzymes in cortical neurons. These all lead potentially to 5-HT and 5-HT$_{2A}$ receptor agonists mediating in conferring neuronal protection against excitotoxic and oxidative stress (adapted from: Fanibunda et al, 2019 PNAS;116(22):11028–11037 www.pnas.org/cgi/doi/10.1073/pnas.1821332116).

PRIMARY TARGET: THE 5-HT$_{2A}$ RECEPTOR (CONT'D)

5-HT$_{2A}$ Receptors and Cognition

The core clinical criteria of an MCI diagnosis include impaired memory and executive dysfunction[105-108]. Acute administration of 5-HT$_{2A}$ agonists can enhance memory and learning[109-118] while administration of 5-HT$_{2A}$ receptor antagonists can impair memory function and learning[113,117,119-125]. By inference, an element of cognitive decline in AD may be associated with the observed decrease in 5-HT$_{2A}$ receptor engagement.

AD-related cognitive impairment can also result from dysfunction of cholinergic and/or glutamatergic neurotransmission[126]. 5-HT$_{2A}$ receptor agonists can experimentally enhance cholinergic neurotransmission and extracellular concentrations of acetylcholine in the hippocampus[127-129]. Similarly, 5-HT$_{2A}$ receptors, expressed on the glutamatergic neurons and glial cells in the brain can influence hippocampal glutamatergic signaling[130]. Thus 5-HT$_{2A}$ receptor agonists like LSD can enhance glutamate release[131,132] and several studies have demonstrated that LSD can acutely enhance memory consolidation in animal models of associative, reversal, and avoidance learning via activation of 5-HT$_{2A}$ receptors in the cortex and hippocampus[110,113,114,133]. These observations support the possibility that LSD could positively benefit MCI/AD outcomes by directly and indirectly modulating neurotransmitter systems in the AD brain associated with cognitive function.

5-HT$_{2A}$ Receptors and Depression and Anxiety

Depression, anxiety, and apathy (collectively referred to as "neuropsychiatric symptoms" or NPS) are reported in 35-85% of MCI patients[134] and are predictors of both MCI and AD[5,135-140]. The relationship between MCI and NPS is complex but appears correlated; conversion to AD is higher in patients with NPS than in NPS-free MCI patients[141]. Conversely, MCI is a risk factor for depression and anxiety[142], suggesting a shared pathobiological mechanism, possibly related to reduced neuroplasticity.

Whether anxiety and depression have a causal role or are symptoms of AD, therapies capable of attenuating NPS in AD are urgently needed. LSD has demonstrated significant antidepressant and anxiolytic effects across a broad dose range (30-350 µg)[143-145], and modern research has further elucidated how 5-HT$_{2A}$ agonists can exert rapid, persistent and clinically relevant antidepressant and anxiolytic effects[146], supporting the therapeutic potential of LSD in MCI and AD patients. Indeed, a recent study in healthy adults showed that microdosed (13 µg) LSD with negligible subjective effects increased neuronal connectivity in limbic circuits associated with depression and anxiety[147].

5-HT$_{2A}$ Receptors, Stress, and the HPA Axis

A connection between 5-HT$_{2A}$ receptor activation and stress is that polymorphisms of the 5-HT$_{2A}$ receptor (*HTR$_{2A}$*) gene correlate with lower stress resilience[148-150]. Further, LSD and other selective 5-HT$_{2A}$ receptor agonists act on stress control pathways by increasing glucocorticoid (GC) levels in animals and humans[151-155]. Stress is a key factor linking depression, anxiety, and MCI[155] and dysfunctional stress responses/dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis are seen in neurodegenerative diseases including AD[4]. In MCI, stress has been associated with chronically elevated GC levels (hypercortisolemia) and abnormal glucocorticoid receptor (GR) expression[156,157], and studies with SSRIs suggest that 5-HT can normalize stress-induced hypercortisolemia[158,159] and increase hippocampal GR expression and neurogenesis via GR-dependent mechanisms[160]. Overall, current understanding of the interaction between 5-HT$_{2A}$ receptor signaling and stress-related psychopathology and impaired neuroplasticity supports the further investigation of 5-HT$_{2A}$ receptor-targeted therapies like LSD to normalize HPA dysfunction in MCI and AD.

SECONDARY TARGETS: ADDITIONAL SEROTONIN AND DOPAMINE RECEPTORS

5-HT_{1A} Receptors

The 5-HT_{1A} receptor is widely expressed throughout the brain. It is expressed at high densities on the cell bodies of serotonergic neurons in the dorsal raphe nucleus (DRN) which produce the bulk of serotonin found in the brain, where it functions as an autoreceptor to sense levels of 5-HT and globally modulate presynaptic cortical release of 5-HT. In cortical tissues, however, 5-HT_{1A} receptors are expressed postsynaptically, whereas 5-HT_{1B} receptors act as autoreceptors to sense local cortical levels of 5-HT. Imaging studies show that there is a significant correlation between 5-HT_{1A} receptor expression, hippocampal hyperactivation, and cortical thinning in AD-relevant brain regions in MCI patients[161,162]. There is a dynamic shift in 5-HT_{1A} expression between MCI and AD; a potential explanation is that in MCI, receptor upregulation may be an early compensatory process to preserve hippocampal function against a conversion to AD, ultimately featuring a loss of 5-HT_{1A} positive neurons and a net decrease in hippocampal expression[162,163].

LSD is a potent partial agonist of 5-HT_{1A} receptor[164-167], and there is preclinical data suggesting that some of the behavioral effects of LSD are mediated through this receptor[167]. Of note is that both 5-HT_{1A} receptor agonists and antagonists demonstrate the capacity to enhance cognition in animal models, suggesting a complex and site-specific role in modulation of neuroplasticity and memory function[168]. Despite these complexities, given the putative benefits already described for LSD mediated through the 5-HT_{2A} receptor as a potential therapy for AD, the current information on 5-HT_{1A} hippocampal function suggests on balance that LSD may also act through the 5-HT_{1A} receptor to help consolidate hippocampal function, and homeostatic balance in MCI, and slow the progression of neurodegeneration[163].

5-HT_6 Receptors

The 5-HT_6 receptor is almost exclusively expressed in the CNS on glutamatergic neurons in the hippocampus and cortex, and modulates excitatory and inhibitory signaling[169-171]. LSD is a potent full agonist of the 5-HT_6 receptor with respect to Gαs pathway signaling[172]. The potential cellular and behavioral effects of LSD acting at this receptor, however, has not been investigated.

5-HT_6 receptor expression substantially declines with age[173], and expression is particularly reduced in AD[174,175]. Antagonists lead to increases in extracellular glutamate, dopamine, acetylcholine, and norepinephrine levels, whereas agonists have no effect on glutamate release but significantly increase cortical GABA extracellular concentrations[176,177]. These findings have led to suggestions that a 5-HT_6 receptor antagonist may ameliorate cognitive dysfunction in mild-to-moderate AD[177]. In large scale clinical trials, however, three different 5-HT_6 receptor antagonists failed to demonstrate therapeutic effects on cognition or other secondary neuropsychiatric endpoints[178,179], and most notably, in mild-to-moderate AD[171].

5-HT_6 receptor agonists, on the other hand, have been shown to reduce levels of Aβ in mouse models of AD[180]. Further, 5-HT_6 receptor agonists can increase hippocampal and cortical BDNF expression as well as expression of the neuroplasticity gene *arc*[181]; and the mixed 5-HT_{1A}/5-HT_6 receptor agonist, hypidone hydrochloride, has procognitive and memory enhancing effects in rodents[182]. Taken together, these data support the idea that an effect of LSD on 5-HT_6 receptors could potentially complement LSD's putative therapeutic benefit to AD as a result of 5-HT_{2A} agonism, although further directed research is required to substantiate this hypothesis.

5-HT_7 Receptors

5-HT_7 receptors are localized anatomically in several brain regions including those responsible for memory like the hippocampus, hypothalamus, and cortex, with high levels found in the suprachiasmatic nucleus[183]. Although LSD has a high affinity for 5-HT_7 receptors, it behaves as an antagonist[183]; however, there is currently no data on whether LSD exerts any promnesic effect through this receptor. Nevertheless, the current incomplete knowledge and questions around 5-HT_7 expression, pathways, and whether it mediates predominantly promnesic or amnesic effects make it an interesting topic for further investigation which may yield new insights into therapies for AD.

Dopamine Receptors in AD and LSD

Dopamine (DA) is a ubiquitous catecholamine neurotransmitter that mediates neuroplasticity and memory function, among others[184,185]. DA modulates synaptic function in the temporal hippocampus as well as memory function in animals via D_2 receptor signaling, whereas blockade of D_2 receptors can impair cognitive function[186].

SECONDARY TARGETS: ADDITIONAL SEROTONIN AND DOPAMINE RECEPTORS (CONT'D)

In postmortem AD brains, D_1, D_3, and D_4 receptor expression is significantly reduced in the cortex, and D_2 receptor expression is moderately reduced in the frontal cortex[187]. In the hippocampus of AD patients, D_2 receptor expression is reduced, and these reductions are associated with cognitive dysfunction[188]. Impaired memory function in rodent models of AD is associated with Aβ burden, which is correlated with decreased cortical DA levels, specifically in the hippocampus[189,190]. These data suggest that hippocampal DA neurons are particularly vulnerable to Aβ toxicity, and that therapies that enhance dopaminergic signaling may attenuate cognitive dysfunction in early AD. For example, in AD patients, D_2 agonists increase cortical excitability, neuroplasticity, and restore central cholinergic transmission[191,192]. Furthermore, the mixed DA receptor agonist apomorphine reduces intraneuronal Aβ and tau levels, attenuates cognitive impairment, and reduces biomarkers of oxidative stress in the 3xTg-AD mouse model[193].

LSD has a moderate affinity for all dopamine receptors, where it acts as an agonist[206,207,208,209]. In addition to direct stimulation, LSD significantly increases D_2 receptor expression and agonist induced signaling indirectly through 5-HT_{2A} receptor activity[194].

Taken together, this evidence suggests that LSD could have a beneficial effect in MCI and possibly in early AD as long as most DA neurons are still intact, by facilitating dopaminergic signaling. That being the case, this would predict LSD to have pro-cognitive therapeutic efficacy in the treatment of MCI and AD.

OVERALL PERSPECTIVES

This review explored the influence of 5-HT_{2A} receptors and potent agonists like LSD on symptoms and pathologies associated with AD, ranging from cognitive decline and neuropsychiatric symptoms, through chronic stress, neuroinflammation and abnormal APP processing to brain IR. We also reviewed the evidence for a role of 5-HT and 5-HT_{2A} receptors in the development of MCI and AD (**FIGURE 5**). It is clear from the various lines of evidence discussed herein, some strong and others more inferential, that selective activation of 5-HT_{2A} combined with mixed activity at several other monoamine receptors can have positive effects in potentially normalizing some of the dysfunctional processes that are known to occur during the development of MCI and progression to AD. LSD itself has recently been studied at low and non-hallucinogenic doses in a small population of older healthy adults and found to be safe and well tolerated[19]. This safety study has established the foundation for follow-on studies of repeated low dose LSD in AD patients to definitively demonstrate clinically meaningful results in the disease modification of AD.

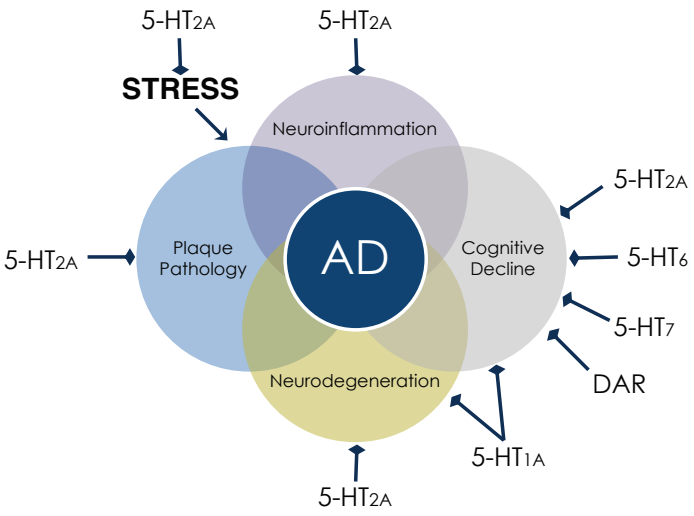

FIGURE 5. Schematic illustrating the potential molecular targets of LSD implicated in the development of MCI and its progression to AD

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